Environmental Chemical Exposures and Risk of Herpes Zoster

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This study investigated whether residence in Aberdeen, North Carolina, the location of the Aberdeen pesticides dumps site (a national priority list Superfund site containing organochlorine pesticides, volatile organic compounds, and metals), is associated with immune suppression as indicated by a higher incidence of herpes zoster and recent occurrences of other common infectious diseases. Study participants included 1,642 residents, 18–64 years of age, who responded to a telephone survey concerning potential occupational and recreational exposures to pesticides and other chemicals, lifetime history of herpes zoster (shingles), and the recent occurrence of other common infectious diseases. Stratified and logistic regression analyses were used to compare the cumulative incidence of herpes zoster among Aberdeen residents and residents of nearby communities. There was little evidence of an overall increased risk of herpes zoster among Aberdeen residents during the period 1951–1994 [relative risk (RR), 1.3; 95% confidence interval (CI), 0.8–2.1]. However, an elevated risk of herpes zoster was noted consistently among Aberdeen residents of younger ages as compared to residents of the nearby communities. The RR was 2.0 (CI, 1.0–4.0) among those 18–40 years of age and was not affected by controlling for potential confounders. The RR of herpes zoster was also consistently elevated in all age groups for the period before 1985. No differences were noted between residents of Aberdeen and those of the nearby communities with respect to the recent occurrence of other common infectious diseases. These results support the plausibility of an association between exposure to the Aberdeen pesticides dumps site and immune suppression and the potential use of herpes zoster as a marker of immune suppression in studies of environmental chemical exposures. *Key words*: environmental, hazardous waste, herpes zoster, immune suppression, organochlorine, shingles. *Environ Health Perspect* 107:835–841 (1999). [Online 9 September 1999]
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Less is known about the effects of environmental exposures on the immune system than about many other adverse outcomes such as cancer. Because the immune system is crucial for the protection of the host against infectious agents and developing neoplasms, enhancement or diminution of any essential immune function could offset the balance necessary for immunoregulation and produce a cascade of secondary effects, including compromised host resistance.

There is a growing awareness that chemicals can influence the activity of the immune system by either augmenting or suppressing its function (*1–3*). Immunosuppressive effects include bone marrow suppression, suppression of lymphocyte response to mitogens and antigens along with termination of suppressed cytotoxic and regulatory T-cell activity, inhibition of stem cell proliferation, decreased natural killer cell activity, and impairment of phagocytic activity (*4*). Evidence from both human and animal studies suggests that pesticides (including organochlorines, organophosphates, and carbamates) (*5–7*), volatile organic compounds (e.g., benzene and toluene) (*8,9*), and metals (e.g., lead, arsenic, methyl mercury) (*2,10–12*) are capable of adversely affecting the immune system.

This paper describes phase 1 of a two-phase cross-sectional study to determine whether residents living in Aberdeen, North Carolina, the location of a national priority list hazardous waste site (the Aberdeen pesticides dumps site) containing organochlorine pesticides, volatile organic compounds, and metals, are more likely than residents of nearby communities to develop immune suppression. In phase 1, the indicator of immune suppression is self-reported episodes of herpes zoster and recent occurrence of other common infectious diseases such as colds and flu. In phase 2, immune suppression is assessed on a subset of participants from phase 1 with a battery of laboratory measures of immune competence such as numbers and types of white blood cells as well as frequency of lymphocyte micronuclei, an indicator of chromosome damage. A previous small study of 41 pet dogs revealed lower CD4/CD8 ratios and higher frequencies of micronuclei among the dogs living in Aberdeen as compared to dogs living in the neighboring towns of Pinehurst and Southern Pines (*13*).

The Aberdeen pesticides dumps site is composed of five sites located in and around the town of Aberdeen in southern Moore County. The five sites include the farm chemicals site (an abandoned pesticide manufacturing/formulating facility where millions of pounds of pesticides were blended or formulated from the mid-1930s to 1987, the most contaminated site); the twin site (a pesticide disposal site located across the street from the farm chemicals site); the fairway six site (a pesticide disposal area); the McIver site (a local landfill into which pesticides and drums were dumped); and the Route 211 site (an old sandmining pit into which pesticides were dumped). Each site is approximately 1 acre in area and all are within 2 miles of each other. Most of the sites were discovered in 1984 or 1985 (*14*).

Near the Route 211 site is another pesticide-contaminated area known as the Geigy Chemical Corporation site. It was the site of chemical and pesticide-formulating companies that made DDT and other chlorinated pesticides from 1947 to 1967 (*15*). Between 1967 and 1989 (when the property was abandoned), it served as a distribution site for the rebagging of prepackaged and bulk chemicals (*16*).

At least 1,000 people live within a 1-mile radius of the sites. Because soils and groundwater at the sites have been contaminated with organochlorine pesticides, solvents, and metals (*17*), there is the potential for human exposure through inhalation, dermal contact, and ingestion of contaminated soils, fish, and groundwater. Public health concerns also arise from the long half-life of some of the contaminants, particularly the organochlorines (*18*).

Herpes zoster (shingles), which is caused by the virus that causes chickenpox, was selected as our primary marker of immune suppression because it has several unique clinical features: *a*) nearly 100% of the U.S. population is infected with chickenpox by the third decade of life (the median age for infection is 5 years) (*19,20*); *b*) the symptoms (itchy water blisters on the skin that crust over and are often painful) are sufficiently severe that they would be remembered; and *c*) studies of persons with known immune

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suppression, such as human immunodeficiency virus (HIV)-infected individuals, people with cancer, and those who have undergone organ transplants, are known to be at increased risk of herpes zoster (*21,22*). In unexposed populations, the incidence of herpes zoster is relatively constant (*21–25*), between 1.5 and 2.5 per 1,000 person-years, and increases with age. If herpes zoster is associated with environmentally induced immune suppression, it may serve as a useful marker of immune suppression in other such studies.

Methods

Study participants. A 15-min telephone survey was conducted between May and August 1994 among residents 18–64 years of age who had lived for at least 1 year in Aberdeen, Pinebluff, Taylortown, or certain sections within and north of Pinehurst, all of which are communities in southern Moore County. Other criteria for inclusion in the study were as follows: residents must have obtained their drinking water from a groundwater source, must have been able to speak English, must have had a listed telephone number, and must not have worked in a pesticide-manufacturing company (because we were interested in residential exposures). Residents in the communities surrounding Aberdeen were also excluded if they had ever lived in Aberdeen. In addition, five individuals were excluded because of implausible data with respect to age, duration of residence, and date or town in which herpes zoster episodes occurred.

Identification of study areas. Residents of Aberdeen were considered those most likely exposed to the contents of the dump sites because all residents lived within approximately 2.5 miles of one of the six dump sites. Criteria for the selection of communities for the comparison areas were as follows: First, the comparison areas had to be located in southern Moore County to control for previous pesticide use in the county and to facilitate data collection. Second, the source of tap water in the comparison areas had to be groundwater because Aberdeen is served by groundwater systems or private wells and there was concern about groundwater contamination as a result of the dump sites. Because groundwater flow is generally southeast, it is unlikely that groundwater contamination in Aberdeen would have affected comparison area residents (*26*). Third, the overall sample of residents in the comparison areas had to be similar with respect to socioeconomic status (mean annual income) and racial composition, based on data obtained from the U.S. Bureau of the Census (Washington, DC) for block group areas in and around Aberdeen. For example, for comparability, only block group areas within Pinehurst with mean annual income < $40,000 were included. Figure 1 displays the study areas and indicates the locations of the dump sites.

Resident identification and enrollment. The majority of the residents within the designated study areas were identified by a mailing list purchased from Telematch, Inc. (Springfield, VA). An additional 10% of residents were identified using the most recent Moore County telephone book, a Polk Directory (The Polk Company, Southfield, MO), and water company records for Aberdeen and Pinebluff. Water company records were not available for the Pinehurst area. A total of 7,830 households were identified in three zip code areas: 7,243 from the mailing list, 94 from the water company records, and 492 from the telephone book.

The final list of potentially eligible households was sorted by street, and streets were identified on local maps. Households were excluded if they were clearly not in one of the study areas or if no phone number was available (< 6%). The majority of households were excluded because they were located in census block groups in Pinehurst with mean income > $40,000.

A total of 3,797 potentially eligible households (1,717 in Aberdeen and 2,080 in the comparison areas) were identified in the selected study areas. A letter explaining the study was mailed to each household before the telephone interview. Interviews were conducted by FGI (Chapel Hill, NC) using a standardized questionnaire with a computer-assisted interview (CATI) system. At least five attempts were made to complete the initial interview in a household. In multirespondent households, a minimum of five additional attempts were made to complete subsequent interviews with eligible household members. Call attempts were made during weekday evenings and on weekends. Some calls were attempted during daytime hours on weekdays.

Households were excluded for the following reasons: disconnected telephone number, business/government, duplicate address, age, length of residence < 1 year, water source not groundwater, and deaf or language problems (Table 1).

Of the remaining 2,179 potentially eligible households (1,025 in Aberdeen and 1,154 in the comparison areas), completed interviews were obtained from 1,447 households, for a household participation rate of 66% [72% (741 of 1,025)] in Aberdeen and 61% (706 of 1,154) in the comparison areas. No further attempt was made to recontact nonrespondents. Information concerning age, race, sex, and number of years of residence in the current town was collected from nonrespondents, but because of a problem with the new CATI software, these data were not retrievable for analysis.

A total of 2,081 residents in the 1,447 participating households were interviewed by telephone. Additional individuals were excluded from the study based on information obtained from the telephone survey. For example, using information about location of residence from the telephone survey, it was determined that 293 individuals (from 206 households) of the 2,081 interviewed did not live in one of the designated study areas. After exclusions, a total of 1,642 study participants remained in the analysis: 900 in Aberdeen and 742 in the comparison areas.

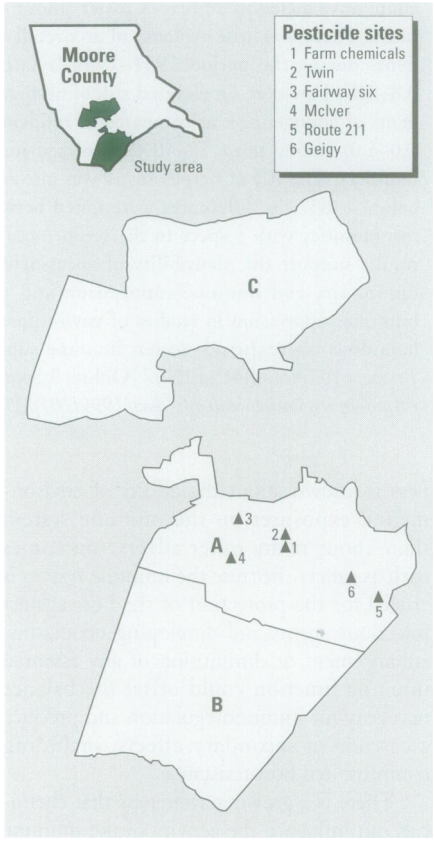

Figure 1. Study areas with dump sites. A, Aberdeen; B, Pinebluff; C, Pinehurst/Taylortown.

Table 1. Reasons for household exclusions.

Reason	Total	Aberdeen	Comparison areas
Total potential households	3,797	1,717	2,080
Disconnected telephone number	382	205	177
Business/government	146	37	109
Duplicate	33	19	14
Age	921	379	542
Length of residence	117	45	72
Water source	8	2	6
Deaf/language problem	11	5	6
Remaining households	2,179	1,025	1,154

Questionnaire. The 15-min telephone questionnaire asked about demographic information (age, race, sex, education, socioeconomic status, and household size), location of current residence (physical street address and nearest intersecting street), length of residence, source of tap water (city or private well), recreational, household and occupational exposures to chemicals including pesticides, smoking habits, and both chronic and acute infectious diseases. Items specific to the potential health effects of exposure to the Aberdeen pesticides dumps site included respiratory and intestinal infections, labial herpes simplex (cold sores), and herpes zoster (shingles). Participants were also asked about history of cancer, in particular leukemia, Hodgkin and non-Hodgkin lymphoma, multiple myeloma, and autoimmune diseases such as lupus and rheumatoid arthritis.

Definition of shingles and case verification. Because herpes zoster is not a common disease, the typical symptoms of herpes zoster were explained to all participants before the participants were asked if they had ever had shingles or zoster or been told that they had this illness. It was explained that shingles is a cluster or group of water blisters that are itchy and crust over, and they are usually limited to a few patches on one side of the body and often are painful. Participants who reported a positive lifetime history of herpes zoster were also asked to report place of residence and date of the last episode of herpes zoster. A second telephone interview was conducted several months later to confirm the information given in the first interview and to obtain further information about all episodes (including year and place of residence where the episodes occurred). Only herpes zoster episodes during adulthood were considered in this analysis for reasons of validity.

Other infectious disease outcomes. Other infectious disease outcomes included whether or not residents had the following infectious diseases within the past 12 months and within the past 2 weeks: cold or flu, sore throat, ear infection, diarrhea, cold sores, and chest infection including bronchitis or (past 12 months only) pneumonia. Residents were also asked the number of times during the past 12 months they had each illness.

Exposure definition. Exposure status was defined by place of residence during the observation period. Each year that a participant was living in the Aberdeen area was counted as an exposed person-year. Living in the comparison areas was considered unexposed time. Also, unexposed status was assumed for the period before participants moved to Aberdeen or the comparison areas. Only person-years during adulthood were counted for both unexposed and exposed periods. Because the duration of illness with herpes zoster is only approximately 1–3 weeks, time with herpes zoster was not excluded from the exposure calculation because it would have had little to no impact on herpes zoster rates.

Potential confounders and effect modifiers. Age (categorized as 18–40 and 41–64 years), sex, race (categorized as white and nonwhite), educational level (≤ 12 years and > 12 years), study period (before 1985 and 1985–1994), occupational pesticide exposure, and exposure to other immunotoxicants were considered potential confounders and/or effect modifiers. Exposure to other immunotoxicants was defined as regular exposure (at least once a week) to substances such as spray cleaners, paints, fumes, solvents, gasoline, silica dust, wood sanding, insulating materials, metal dust or fumes, ionizing radiation, or other chemicals. Other covariates that were considered included income, smoking status, various illnesses, pesticide exposure at home, pesticide exposure due to recreational activities, and use of steroids.

Statistical analyses. Study participants from Aberdeen and the comparison areas were compared with respect to the distribution of potential confounding attributes: sociodemographic factors, smoking, health status, pesticide exposure at home and/or at work, or exposure to other potential immunotoxicants. Stratified analyses were performed to evaluate modification and confounding [by age, sex, race, education, occupational pesticide exposure (farm work), exposure to other potential immunotoxicants, and study period] on the person-year rate ratio (RR) for the effect of residence on the occurrence of herpes zoster. The joint effect of place of residence, age, sex, race, occupational factors, and study period was assessed by multiplicative logistic regression (*27*). Likelihood ratio tests were performed to test for two-factor interaction between living in the exposed area and each of the covariates (α = 0.05). Stratified and logistic regression analyses were also performed to determine whether town of residence was associated with the prevalence and number of episodes of other common infectious diseases controlling for potential confounders.

Results

Descriptive characteristics of the population. On average, participants in Aberdeen were 41.9 years old and had lived there for 16.6 years (Table 2). They were predominantly white and the majority had > 12 years of education. Also, a majority had a positive lifetime history of smoking and approximately 25% ever used steroids.

Residents from the comparison areas tended to be older (mean age: 44.3 years) but to have lived less time in their current town of residence (mean: 12.1 years). This is explained by the fact that many retirees recently moved to the comparison areas. The proportion of whites and of persons with > 12 years of education was higher in the comparison areas.

Of diabetes, cancer, lupus, arthritis, asthma, and hay fever, only diabetes was significantly more prevalent among Aberdeen residents as compared to people in the neighboring communities controlling for age and sex.

Exposures to pesticides and immunotoxicants. Pesticides were used in almost every Aberdeen household to treat homes for termites, bugs, insects, or fleas. Approximately 50% of the Aberdeen participants reported the use of powders, collars, shampoos, or dips to control fleas or ticks on pets, and more than one-third applied pesticides to control weeds or bugs in the garden or on the lawn. Approximately one-third of all Aberdeen participants had ever worked in a job with potential pesticide exposure, such as farmer/farm worker, gardener, or pesticide formulator (in order of frequency). Approximately 50% of the Aberdeen participants reported regular exposure (at least once a week) to one or more other immunotoxicants, mainly volatile organic chemicals such as spray cleaners, paints, fumes, solvents, or inert materials such as silica dust, sawdust, and insulating materials.

The comparison area residents were less exposed to pesticides at work and at home because there was a higher proportion of farmers in Aberdeen and Aberdeen residents were more likely to use pesticides on pets. Regular exposure to other potential immunotoxicants was also less common among the comparison group. The observed difference was mainly due to their lower exposure to volatile organic chemicals found in spray cleaners, paints, fumes, solvents, and gasoline. Factors such as farming, use of pesticides on pets, and exposure to other chemicals were taken into consideration in the analysis.

Occurrence of herpes zoster. In total, 64 episodes of herpes zoster were reported from the study participants who were 18–64 years of age. Forty-eight participants stated that they had herpes zoster once, six twice, and one participant reported four episodes. The crude rates show a 50% increased risk for Aberdeen residents as compared to residents living in the comparison areas. However, after controlling for age this difference diminished (Table 3). Incidence of herpes zoster was reported more often for recent years than for earlier years and the increase over time was independent of age.

No difference in rates of herpes zoster was seen between men and women. White study

participants had higher rates for herpes zoster than nonwhites. The risk of herpes zoster increased with an increase in age. Smoking status showed no association with the risk of herpes zoster after controlling for age. Higher education was associated with a weak increased risk.

Herpes zoster was more often found among participants who reported steroid use or regular exposure to potential immunotoxicants, in particular, spray cleaners, silica dust, or radiation (Tables 3 and 4). Indoor use of pesticides and potential occupational exposure were associated with an increased risk for herpes zoster. The association between herpes zoster and occupation was most prominent for farmers or farm workers.

Table 2. Descriptive characteristics of the population in the telephone survey study.

Characteristic	Aberdeen (n = 900)	Comparison areas (n = 742)	p-Value*
Age (mean ± standard error)	41.9 ± 0.4 years	44.3 ± 0.5 years	0.0002**
Duration of residence (mean ± standard error)	16.6 ± 0.5 years	12.1 ± 0.5 years	0.0001**
Male	40.8%	45.3%	0.07
Nonwhites	17.8%	14.0%	0.04
Education: up to high school	43.3%	37.8%	0.03
Annual income < $30,000	35.4%	27.6%	0.001
Ever smoked	54.0%	54.2%	0.96
Ever used steroids	25.0%	26.4%	0.53
Indoor use of pesticides	85.4%	84.9%	0.76
Use of pesticides for pets	51.2%	42.5%	0.001
Use of pesticides for lawn and weeds	37.2%	41.2%	0.10
Ever worked in a job with potential pesticide exposure	32.2%	29.9%	0.32
Gardener	10.4%	11.5%	0.46
Farmer/farm worker	20.2%	15.9%	0.03
Pesticide formulator	5.2%	5.6%	0.70
Other	9.3%	10.3%	0.49
Regularly exposed to potential immunotoxicants	49.6%	42.9%	0.007
Spray cleaners, paints, fumes, solvents, gasoline	34.5%	29.1%	0.02
Silica dust, sawdust, insulating materials	17.5%	16.5%	0.58
Metal dust or fumes	11.0%	10.8%	0.86
Radiation, x-rays	7.9%	7.6%	0.81
Other chemicals	13.5%	13.5%	0.97

*p-Value derived from χ^2 statistic comparing Aberdeen and comparison areas. **p-Value derived from t-test statistic (two-sided).

Table 3. Risk of herpes zoster dependent on study population characteristics.

Characteristic	Events	Person-years	Crude rate (per 100,000 person-years)	Relative risk, age adjusted[a]
While living				
In Aberdeen	24	12,154	197	1.3 (0.8–2.1)
Not in Aberdeen	40	30,556	131	1
Study period				
Before 1985	19	27,182	70	1
1985–1994	45	15,528	290	3.4 (2.0–5.8)
Sex				
Male	27	17,973	150	1
Female	37	24,737	150	1.0 (0.6–1.6)
Race				
White	58	35,725	162	1
Nonwhite	6	6,484	93	0.6 (0.3–1.4)
Age				
18–40 years	31	31,088	100	1
41–64 years	33	11,622	284	2.9 (1.8–4.6)
Smoking				
Never	31	17,784	174	1
Ever	33	24,447	135	0.7 (0.5–1.2)
Education				
Up to high school	24	18,085	133	1
More than high school	40	23,918	167	1.4 (0.8–2.3)
Annual household income				
< $30,000	20	12,959	154	1
≥ $30.000	42	26,959	156	1.0 (0.6–1.8)
Use of steroids				
Never	33	30,193	109	1
Ever	30	11,404	263	2.4 (1.4–3.8)

[a]95% confidence intervals in parentheses.

Stratified analysis. Stratified analysis was performed to evaluate modification and confounding of the association between place of residence and risk of herpes zoster by age, sex, race, education, occupational factors, and time period (Table 5). Stratification by age revealed stronger associations among younger residents. Additional stratification by potential confounders yielded small cell counts with wide confidence intervals but, in general, the impact of place of residence on the risk of herpes zoster appeared to be stronger among younger ages (18–40 years). The data also suggest a stronger effect of residence in Aberdeen for the period before 1985, when pesticide manufacturing plants were operating and before any remediation efforts took place. However, an elevated risk among younger Aberdeen residents was also noted during the last decade of the study period. Overall, the effect of place of residence on the risk of herpes zoster seems stronger among white male participants with higher education who have not worked on a farm.

Multivariate analysis. Because age and time period appear to act as effect modifiers, age- and period-specific relative risk estimates adjusted for the joint effect of the other covariates were calculated using multiplicative logistic regression (Table 6). The risk of herpes zoster seemed higher for both younger and older Aberdeen residents as compared to residents from nearby communities before 1985. A slight increase in risk was also found for the residents 18–40 years of age for the last decade of the study period. However, the data also suggest a decreased risk among older residents living in the exposed area during that decade. Controlling for age as a continuous variable or restricting the analysis to the first episode of shingles had little effect on the relative risk estimates.

No association was noted between town of residence and the prevalence or the number of episodes of other common infectious diseases after controlling for age, the number of children in the household < 6 years of age, household size (> 2 individuals yes/no), income > $30,000, education, race, sex, and current smoking status.

Discussion

The telephone survey study does not provide strong evidence for an overall immunosuppressive effect of environmental exposure among Aberdeen residents. However, among residents 18–40 years of age (vs. 41–64 years of age), Aberdeen residents were two times more likely to develop herpes zoster (shingles) as compared to residents of nearby communities. Those living in Aberdeen during the period before 1985 (when pesticide

manufacturing facilities in Aberdeen were still in operation and before any remediation efforts took place) were 2–3 times more likely to have reported episodes of herpes zoster among all age groups than those living in nearby communities. There was no evidence of a difference in the occurrence of other recent infectious diseases among exposed and nonexposed communities.

A plausible explanation for the age effect might be that age itself is such a strong risk factor for herpes zoster that the additional effect of the given exposure is too small to result in any detectable difference among older adults when unexposed and exposed participants are compared. Another explanation for the stronger effect among younger residents might be that younger people may have been more exposed to environmental sources of pesticides because of increased recreational outdoor activity. It is also possible that many older retirees in Pinehurst have less contact with their extended families; therefore, they are less exposed to children with chickenpox than older persons in Aberdeen. Because contact with infectious carriers of the chickenpox virus boosts zoster-specific immunity among immunocompetent persons (*28*), older persons in Aberdeen may have better zoster-specific immunity than many older persons in the comparison areas.

The increased risk of herpes zoster among Aberdeen residents before 1985 as compared to the recent decade might be due to the higher pesticide exposure during the earlier years, when most of the facilities were still in use. However, a slight but statistically nonsignificant increase in risk was still seen among the younger Aberdeen residents for the 1985–1994 time period. In contrast, no increased risk was seen among older Aberdeen residents during the last decade.

Because the participants in this study were surveyed at one point in time, it is possible that heavily exposed individuals who moved to other places might be missing from our study population. This potential selection bias would likely result in underestimating any effect of environmental exposure. We controlled for residential mobility among the study participants by assigning individual exposure status for each year, but we were unable to control for the fact that former residents in both communities may have moved before this study. The inclusion of Pinehurst residents in the comparison group could have increased our chances of finding a positive result if Pinehurst residents were healthier than Aberdeen residents in general. Controls for race, education, and income were intended to minimize such an effect. Furthermore, of a variety of diseases assessed, only diabetes was more prevalent among Aberdeen residents than among comparison area residents controlling for age and sex. Data from our study do not indicate that diabetics are more prone to herpes zoster than others (data not shown).

The small number of cases is the main limitation of this analysis, but the numbers are large enough to yield findings that correspond to published data regarding the incidence of herpes zoster. In normal populations, the incidence of herpes zoster is approximately 1.5–2.5 per 1,000 person-years (*21–25,29*), which is close to the rate observed in our study during the last decade.

Donahue et al. (*29*) reported a 2-fold increase in the age-adjusted rates of herpes zoster during the last 30 years based on health maintenance organization records. Immune suppression is a well-known risk

Table 4. Risk of herpes zoster dependent on potential household and occupational pesticide or other immunotoxicant exposure.

Potential exposure	Events	Person-years	Crude rate (per 100,000 person-years)	Relative risk, age adjusted[a]
At home				
No	4	5,231	76	1
Yes	60	37,479	160	2.1 (0.8–5.6)
For pets				
No	35	24,607	142	1
Yes	29	18,103	160	1.3 (0.8–2.1)
For lawn and weeds				
No	40	25,053	160	1
Yes	24	17,657	136	0.8 (0.5–1.4)
Ever worked in a job with potential pesticide exposure				
No	37	29,815	124	1
Yes	27	12,895	209	1.8 (1.1–2.9)
Gardener	5	3,707	135	0.9 (0.3–2.4)
Farmer/farmworker	21	7,985	263	2.2 (1.3–3.8)
Pesticide formulator	2	1,929	104	0.5 (0.1–2.2)
Other job	11	3,865	285	2.0 (1.0–4.0)
Exposure to immunotoxicants				
No	30	24,246	124	1
Yes	34	18,464	184	1.6 (1.0–2.6)
Spray cleaner	23	12,070	191	1.4 (0.8–2.5)
Silica dust	13	6,349	205	1.3 (0.6–2.6)
Metal dust	5	4,092	122	0.6 (0.2–1.6)
Radiation	9	3,061	294	2.1 (1.0–4.3)
Other chemicals	11	5,339	206	1.4 (0.7–2.7)

[a]95% confidence intervals in parentheses.

Table 5. Age-specific and overall rate ratios and 95% confidence intervals for herpes zoster episodes comparing residence in Aberdeen versus elsewhere.[a]

Characteristics	18–40 years (31 cases)	41–64 years (33 cases)	Crude (64 cases)	Age-adjusted	p_{BD}
Overall	2.0 (1.0–4.0)	0.9 (0.4–1.8)	1.5 (0.9–2.5)	1.3 (0.8–2.1)	0.11
Sex					
Male	3.2 (1.2–8.7)	1.1 (0.4–3.4)	2.2 (1.0–4.5)	1.9 (0.9–3.9)	0.17
Female	1.3 (0.5–3.6)	0.7 (0.3–1.8)	1.2 (0.6–2.3)	0.9 (0.5–1.8)	0.43
Race					
White	2.5 (1.2–5.3)	0.9 (0.4–1.8)	1.7 (1.0–2.8)	1.4 (0.8–2.3)	0.05
Nonwhite	0.5 (0.0–4.5)	2.8 (0.1–68.7)	0.8 (0.2–4.6)	0.9 (0.1–5.5)	0.26
Education					
Up to high school	2.6 (0.6–12.3)	0.7 (0.3–1.9)	1.4 (0.6–3.2)	1.0 (0.5–2.2)	0.17
More than high school	2.0 (0.9–4.5)	1.0 (0.3–2.9)	1.6 (0.9–3.1)	1.5 (0.8–2.9)	0.31
Annual income					
< $30,000	1.9 (0.5–7.0)	1.2 (0.4–4.1)	1.9 (0.8–4.4)	1.5 (0.6–3.6)	0.63
≥ $30,000	2.0 (0.9–4.7)	0.6 (0.2–1.8)	1.3 (0.7–2.5)	1.2 (0.6–2.2)	0.09
Farmer/farm worker					
No	3.2 (1.5–7.1)	0.7 (0.3–1.8)	1.7 (1.0–3.2)	1.5 (0.8–2.7)	0.01
Yes	0.3 (0.0–2.5)	0.9 (0.3–2.8)	1.0 (0.4–2.4)	0.7 (0.3–1.8)	0.41
Other potential immunotoxicants					
No	2.7 (0.9–7.7)	0.9 (0.3–2.4)	1.7 (0.8–3.5)	1.4 (0.7–2.9)	0.13
Yes	1.5 (0.6–4.1)	0.8 (0.3–2.2)	1.4 (0.7–2.7)	1.1 (0.6–2.2)	0.37
Study period					
Before 1985	1.6 (0.5–5.1)	3.6 (0.7–19.2)	2.2 (0.9–5.4)	2.1 (0.8–5.3)	0.46
1985–1994	1.5 (0.6–4.0)	0.6 (0.3–1.2)	0.9 (0.5–1.6)	0.8 (0.5–1.5)	0.10

BD, Breslow day statistic.
[a]Stratified by sex, race, education, income, occupational exposure, and study period.

Table 6. Descriptive characteristics and age-specific rate ratios and 95% confidence intervals for herpes zoster during different study periods comparing residence in Aberdeen versus elsewhere.[a]

Study period	Age range	Subjects (no.)	Person-years	Shingles episodes (no.)	Ages at shingles episodes	Shingles episodes (years)	Crude rate (per 100,000)	Adjusted rate ratio[b]
Entire period	18–40	1,642	31,088	31	18–40	1951–1994	100	2.1 (1.0–4.3)
	41–64	910	11,622	33	41–62	1978–1994	284	0.7 (0.4–1.5)
Before 1985	18–40	1,434	22,751	14	18–38	1951–1984	62	1.8 (0.5–5.7)
	41–64	525	4,431	5	42–52	1978–1982	113	3.2 (0.4–23.4)
1985–1994	18–40	1,081	8,337	17	22–40	1985–1994	204	1.6 (0.6–4.1)
	41–64	910	7,191	28	41–62	1985–1994	389	0.5 (0.2–1.1)

[a]Adjusted with multiplicative logistic regression controlling for sex, race, education, income, farm work, and exposure to other potential immunotoxicants. [b]Aberdeen versus comparison areas.

factor for herpes zoster. The increasing use of immunosuppressive therapy in the treatment of patients with such conditions as cancer and asthma, and the rising number of recipients of organ transplants, may explain a portion of the increase in the incidence of herpes zoster during the last decades (*29*). Herpes zoster episodes among our study population seemed to increase even more during the last three decades. Because our data rely on self-reports, incomplete recall of former episodes may augment any underlying emerging trend. Although better recall of herpes zoster episodes among Aberdeen residents than among those in comparison areas could theoretically account for the positive associations seen in this study, it is not clear why earlier episodes (those at younger ages and episodes before 1985) might be remembered to a different extent among Aberdeen and comparison area residents. Furthermore, no consistent associations were seen between place of residence and other self-reported diseases.

Although the small sample size limited both the range of outcomes and the size of effects that could be studied, statistically significant associations between herpes zoster and age and steroid use provide some assurance that this study has the power to detect associations found in other studies. With 900 exposed and 742 unexposed participants and 4.5% of cases among the unexposed, the study had an 80% power to detect an overall RR of 1.8 (α = 0.05). One thousand study participants per age/period group would have been needed to detect a RR of 2.0 in subgroup analyses.

Exposure to radiation and, to some extent, exposure to other immunotoxicants were also strongly associated with herpes zoster. However, because respondents were surveyed at one point in time, it is not clear whether these exposures preceded or followed herpes zoster episodes. Although the incidence of zoster is most notably increased in severe immunodeficiencies such as HIV infection and immunosuppressive therapy (*21,22*), less marked immune suppression, such as that which occurs in older populations, is also manifest by an increased risk of herpes zoster.

Racial differences in the occurrence of herpes zoster have been described recently (*30*), indicating a higher risk of zoster among whites than among African Americans, which is in agreement with our findings. As with the current study, no significant differences with respect to sex or education have been reported in most studies.

The normal immune response in humans is heterogeneous, making it difficult to discern a subtle adverse effect without a large experimental cohort. Similarly, adverse health effects that only result in subclinical immune dysfunction in humans are difficult to assess. Persons living in any given area are usually heterogeneous, either with respect to characteristics that can influence many health outcomes independently of exposure (age, race, socioeconomic status, occupation, smoking, alcohol consumption, etc.) or with respect to the type, level, duration, or timing of exposure. Exposure in this study was considered years of residence in Aberdeen, whereas only a subset of residents may have actually been exposed to the contents of the dump sites depending on where in Aberdeen they lived, potentially leading to an underestimate of the effect of exposure on risk of herpes zoster. Moreover, there is migration and geographic mobility within the areas. We tried to address these concerns by multivariate analyses, controlling for calendar-time and determination of individual time at risk. Uncertainty of the temporal sequence of exposure and disease is a concern when data arise from a cross-sectional survey. In this study, however, at least 1 year of exposure preceded each herpes zoster episode among Aberdeen participants. We also considered major potential confounders such as demographic characteristics, smoking, medications (such as steroid use), illnesses, and occupational and recreational sources of pesticide exposure. However, because it was a cross-sectional study, it is not clear whether some potential confounding exposures preceded episodes of herpes zoster. Other potential risk factors for herpes zoster for which there is only limited evidence, such as recent stress, poor diet, and lack of sleep, were not assessed.

Conclusion

Although the association between exposure to the Aberdeen pesticides dumps site and immune suppression was not assessed directly, data from this study support the plausibility of such an association, especially among younger residents and during the period before 1985. Results also suggest that herpes zoster has the potential to serve as a marker for immune suppression in future studies of environmental chemical exposures and effects on the immune system despite small sample sizes and self-reported herpes zoster episodes.

Although evidence for pesticide-induced immune suppression exists from experimental animal studies (*6*), only limited examples of pesticides that cause clinical adverse health effects of immune suppression in humans have been found (*31*). This may be due in part to the lack of sensitivity of routinely used measurements of immune function and to the diversity of responses observed in those tests among exposed individuals. It is also possible that the normal exposure levels are too low to result in any detectable effect. Furthermore, the immune system contains redundancies and backups so that any given abnormality may be compensated for by other functional pathways (*32*). Biologically relevant effects may occur only after the functional reserve capacity has been exceeded (*33*). Clearly, more research in the area of chemical-induced immune suppression is warranted.

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